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08/816,122

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/816,122	03/11/97	BUSH	A 0609.435000

EXAMINER: DUFFY, P.

HM21/0818

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ART UNIT	PAPER NUMBER
1645	11

DATE MAILED: 08/18/98
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5-4-98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-39 is/are pending in the application.
Of the above, claim(s) 1-20 + 24-39
☐ Claim(s) _____ is/are withdrawn from consideration.
☒ Claim(s) 21-23 is/are allowed.
☐ Claim(s) _____ is/are rejected.
☒ Claim(s) 1-39 is/are objected to.
_____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents heve been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of e claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice to Comply with Sequence Rules.
☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5+8
☐ Interview Summery, PTO-413
☒ Notice of Dreftperson's Patent Drewing Review, PTO-948
☐ Notice of Informel Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

Sequence Requirements

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. For example, Figure 10 contains an amino acid sequence. This sequence is not followed by a proper sequence identifier and is not separately listed in a sequence listing nor identified by the sequence identifier in the Brief Description of the Drawings. Full compliance with the sequence rules is required in response to this office action.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings are objected to by the draftsperson under 37 C.F.R. 1.84 or 1.152. See PTO-948 for details. Correction of the noted defects can be deferred until the application is allowed by the examiner.

Election/Restriction

3. Claims 1-20 and 24-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions. Election was made **without** traverse in Paper No. 10, mailed May 4, 1998.

Claim Rejections - 35 USC § 112

4. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Briefly, the claims are drawn to a method of identifying an agent to be used in the treatment of Alzheimer's Disease. The claims are not enabled for the reasons set forth below.

The role of amyloid precursor protein (APP) processing in the generation of Alzheimer's Disease is controversial. Several theories have been set forth which include the increased production of APP fragments and the aberrant metabolism of APP and the production of oxidative stress and toxic reactive oxygen intermediates. The art is controversial with respect to the role of APP and fragments thereof as either the cause or the effect of the primary disease process, and this issue remains to be resolved at this time (Borman, S, Science, June 17, 1996 pages 33-34). Moreover, the deposition of APP fragments in cerebral plaques is not the only neuropathological feature of Alzheimer's Disease. Alzheimer's patients also display a significant neurofibrillary tangle (NFT) component which has been also been strongly implicated in neuronal dysfunction and deterioration (Sisodia et al , Neurodegenerative Diseases, 5(1):59-68, 1995 and Smith et al, Neuropathology and Applied Neurobiology, 20:322-338, 1994). Thus, it is not clear that affecting the generation of superoxide by Aβ would predictably identify effective therapeutic compounds or correlate with the amelioration or exacerbation of any of the classical neurophysiological parameters of Alzheimer's Disease, such that effective therapeutics can be predictably and reproducibly identified using the instantly claimed screening assay. One skilled in the art would have reason to doubt that effective or candidate therapeutics could be identified

using the instant screening assay because the art has demonstrated that inhibitors of free radical formation (i.e. the instant superoxide, O_2-) failed to attenuate direct Aβ peptide-mediated neurotoxicity (Lockhart et al, J. Neurosci. Res., 39(4):494-505, 1994).

The specification is fails to teach or measure the actual generation of superoxide by amyloid peptide as compared to any appropriate buffer and non-specific peptide control(s). Thus, it is not clear from the teachings of the specification that Aβ is responsible for the generation of superoxide in buffer. The specification is inconsistent in the analysis of what is required in the assay to measure superoxide, for example at page 11,

> "Additionally, $A\beta_{1-42}$, but not $A\beta_{1-40}$ recruits O_2 into spontaneous generation of another ROS, O_2-, which also occurs in a metal dependent manner."

however, later in the specification at page 48, the specification teaches that:

> ".... Aβ can spontaneously produce superoxide radical (O_2-) in the absence of metal ions."

Thus, the specification is inconsistent on the particular conditions and reagents which are required to perform the pharmaceutic screening assay. The specification provides no working examples of the formation and measurement of superoxide by Aβ. The specification *speculates* that reduction of reactive oxygen species (ROS) leads to decreased neurotoxicity and thus provides for a therapeutic screen. However, this is in direct contrast to the art which inhibitors of free radical formation (i.e. the instant superoxide, O_2-) failed to attenuate direct Aβ peptide-mediated neurotoxicity (Lockhart et al, J. Neurosci. Res., 39(4):494-505, 1994). The specification fails to teach any single agent which in the assay reduces superoxide generation by Aβ and performs as an effective agent in the treatment in Alzheimer's disease. The specification fails to teach that the instantly claimed decreased level of superoxide generation by

Aβ predictably and reproducibly correlates with any known therapeutic compounds or other successful therapeutic intervention of Alzheimer's Disease as assessed by any conventional assessment means of neurophysiological or neuropsychological parameters in humans or any other animal models of amyloidosis. The *in vitro* data presented for metal-dependent generation of hydrogen peroxide by Aβ does not speak to the predictability and reproducibility of the *in vivo* therapeutic effectiveness of compounds which inhibit the process because the specification fails to teach that any compound identified by this process is effective to treat Alzheimer's disease *in vivo*. Moreover, for the sake of argument, even if the specification had demonstrated that a compound exhibited a corresponding decrease in the production of superoxide, the specification still fails to teach that the decrease positively correlates with a demonstrated therapeutic benefit which would be expected by the skilled artisan for a compound which was claimed effective for treating Alzheimer's disease. Compounds that are effective for treating Alzheimer's disease would be expected to exhibit therapeutic benefit such as amelioration of symptoms or reversal of the disease process. However, the specification fails to teach that known compounds (i.e. tacrine) effective for treating Alzheimer's disease as instantly claimed such that one of skill in the art could predictably and reproducibly identify other potentially effective compounds by performing the instantly claimed assay.

For the foregoing reasons, in light of the controversy in the art regarding the role of Aβ in neurotoxicity and Alzheimer's Disease, the lack of a predictable and reproducible therapeutic correlation of an effective compound with an decrease in the generation of superoxide by Aβ, it would require undue experimentation on the part of the skilled artisan to practice the invention as is instantly claimed.

Pertinent Prior Art

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hensley et al (Proc. Natl. Acad. Sci., 91:3270-3274, 1994) teaches theat salicylate hydroxylation assays indicate that reactive oxygen species are generated by the β-amyloid-(25-35) fragment during cell free radical-based incubation for a limited very short period of time (see page 3273, Figure 6). Hensley et al is silent on the type of reactive oxygen species of free radicals generated and does not provide motivation to screen for inhibitors of superoxide production by Aβ in a cell free system.

Status of Claims

6. No claims are allowed.

7. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Patricia A. Duffy, Ph.D.
August 16, 1998

Patricia A. Duffy, Ph.D.
Patent Examiner

Group 1600

Application No. 08/816,122

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821-1.825. Applicant's attention is directed to these regulations, published at 114 C 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of tl marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. Other: _____

Applicant must provide:

☒ An (initial) ~~or substitute~~ computer readable form (CRF) copy of the "Sequence Listing"

☒ An (initial) or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the sa and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contac

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.